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GRADE-based procalcitonin guideline for emergency departments

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ABSTRACT

Procalcitonin is a useful biomarker for infection. Over the past two decades, there has been much research on the clinical applications of procalcitonin, yet the majority of these studies have been conducted in the intensive care setting. Despite the extensive use of procalcitonin in emergency departments, there have been no guidelines focusing specifically on these clinical settings. Additionally, previous guidelines were predominantly shaped by expert consensus and rarely incorporate evidence-based medicine concepts. To address these shortcomings, the

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SHOUT
SHARE
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Keywords:
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Antibiotic stewardship
Septic patients
Diagnostic performance
Molecular testing
Guideline

current guideline adopts a novel approach. Initially, we identified the most critical questions regarding the use of procalcitonin in emergency settings through expert voting. This was followed by a systematic literature review and the evaluation of evidence levels using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology. Key characteristics of individual studies will be summarized and evaluated by the guideline development group to determine the overall quality of evidence. The GRADE working group's categorization system will be employed to rate evidence quality into four levels. Recommendations will be formulated based on explicit consideration of established criteria. This structured approach ensures that guideline recommendations are founded on robust evidence and transparently assessed for strength and potential caveats. This is the first guideline on the use of procalcitonin to be applied in emergency departments that adopts the principles of evidence-based medicine and encompasses the up-to-date literatures, and it marks an advancement in providing guidance on the utilization of procalcitonin in emergency departments.
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1. Introduction

Multidrug-resistant bacterial infections have become a significant clinical and public health concern, especially due to the increasing use of antibiotics, one of the most dominant risk factors for the emergence of these resistant strains. This misuse of antibiotics can be connected to the many issues surrounding clinical antibiotic use. In fact, early differentiation between bacterial and viral infections, as well as the dynamic evaluation of antibiotic treatment efficacy, remain major clinical challenges. Clinical presentations, white blood cell counts, and image findings can be influenced by patient comorbidities, trauma, surgical status, and the use of steroids or immunosuppressive therapies. Furthermore, microbial cultures take time and are often complicated by the presence of contaminants and colonizing bacteria.

Procalcitonin (PCT) is the precursor of calcitonin secreted by the thyroid C cells [1]. In healthy individuals, PCT is usually undetectable (<0.01 ng/mL). When the body is stimulated by endotoxins, PCT is rapidly produced by the body's solid organ tissues. It can be detected as early as 2–4 h after an infection, with a half-life of approximately 24 h in the body [2,3]. PCT production can be observed in various types of bacterial infections [4,5]. During aseptic inflammatory responses or viral infections, PCT levels might also increase, but this is not common [6]. These characteristics make PCT an effective biomarker for diagnosing bacterial infections, and monitoring PCT levels dynamically can also benefit the differential diagnosis of infections and assist in monitoring the resolution of the infection and antibiotic stewardship.

PCT has been utilized in the management of various infectious diseases and, based on numerous high-quality clinical studies, expert consensus on PCT-guided antibiotic use has been published. Even though, those studies were mainly conducted in the intensive care setting, PCT also plays an important role in the emergency department. Moreover, antibiotic management protocols based on the Asia-Pacific consensus have been established for both critical and non-critical situations [7,8]. The clinical environment in Taiwan has its unique characteristics, and there is an urgent need to promote the use of PCT. The goal is to enhance adherence to PCT-guided antibiotic use protocols in various clinical situations, assisting physicians in making more precise decisions in the emergency department settings. In light of this, Taiwanese experts have compiled this expert consensus guideline. This guideline further consolidates existing clinical evidence, addressing as comprehensively as possible the common questions regarding the clinical application of PCT, offering evidence-based suggestions encompassing the latest literatures by GRADE method. The purpose of this guideline is to provide Taiwanese physicians with recommendations on the clinical use of PCT for diagnosing infections and guiding antibiotic use in the emergency department. However, PCT cannot replace a thorough clinical evaluation including detailed medical history, symptoms, signs, laboratory, and imaging findings. The suggestions in this guideline, thus, cannot substitute a physician's judgment for specific patients and unique clinical situations. Physicians may choose to voluntarily follow the guidelines, making final decisions based on the individual patient's situation.

2. Methods

This guideline committee was convened by the Taiwanese Society of Emergency Medicine and consists of 15 experts from relevant fields. Initially, these 15 committee members selected the five most clinically relevant topics related to PCT from a list of ten. Subsequently, a core working group comprising C-C Lee, Y-T Lee, and K-F Chen guided medical students in conducting systematic literature reviews. The literature search was limited solely to clinical studies, while excluding case reports, commentaries, literature review articles, and guidelines, with no restriction on publication date, language or region. The keywords used for searching are mentioned in later sections. In addition to the direct search results from electronic medical databases, references from these articles were also considered as data sources.

The meta-analysis reviews in this document were evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology to determine the evidence quality levels [9]. The levels of quality were divided into four grades: high (4 to 3.5 points), moderate (3 to 2.5 points), low (2 to 1.5 points), and very low (below 1.5 points). The meta-analysis reviews represented the highest level of evidence; hence, they started at the high evidence level (4 points) and were downgraded from there. Factors for downgrading included the following five: risk of bias, indirectness, inconsistency, imprecision, and publication bias. The criteria for evaluating each downgrading factor were as follows:

1. **Risk of Bias:** For diagnostic accuracy studies, this evaluated the risk of bias section in the QUADAS-2 [10] scale of the meta-analysis reviews. If the review displayed the QUADAS scale, then each risk item corresponded to the four key domains of QUADAS-2. If the high-risk section was less than 1/3, it was rated as “not serious” and it was not downgraded; between 1/3 to 2/3, it was rated as “suboptimal” and it was downgraded by 0.5 points; and more than 2/3, it was rated as “serious” and it was downgraded by 1 point. The “unclear” section of the scale was not considered for downgrading, and the total downgrade for the four key domains was capped at 1 point. For studies that were not diagnostic accuracy studies, we evaluated the risk of bias section of the meta-analysis reviews, and used the Jadad scale to assess the risk of bias in randomized controlled trials.
2. **Indirectness:** This evaluated the applicability section of the QUADAS-2 scale in the meta-analysis reviews. If the high-risk section was less than 1/2, it was deemed “not serious” and it was not downgraded. If it was more than 1/2, it was deemed “serious” and it was downgraded by 0.5 points. If the review presented the QUADAS scale, then we assessed whether the study population differed significantly from the emergency patient population. If not, it was not included in the downgrade criteria.
3. **Inconsistency:** This evaluated the heterogeneity of the meta-analysis reviews. If I^2 was above 50 %, it was downgraded by one level. If I^2 was below 50 %, it was not downgraded.

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4. **Imprecision:** This assessed the statistical data of the meta-analysis reviews, including OR (Area Under the Receiver Operating Characteristic curve), and DOR (Diagnostic Odds Ratio). If the estimated values for sensitivity, specificity, or AUROC were below 0.5, or the confidence interval width was more than 0.5, or the confidence interval for DOR included 1, then any of the aforementioned conditions were deemed "serious" and it was downgraded by 1 point.
5. **Publication Bias:** This was primarily evaluated by assessing whether the *p*-value of Deek's test was less than 0.05. If so, then it was considered "serious" and it was downgraded by 0.5 points.

Upgrade factors included the following three items: strong effect, dose-response gradient, and whether all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. After comprehensive evaluation, high evidence levels included meta-analysis and individual randomized clinical trials. Medium evidence levels included downgraded randomized clinical trials and upgraded observational studies. Low evidence levels included high-quality observational studies, while very low levels consisted of low-quality observational studies and expert opinions. The 3-expert core working group unified the standard reading criteria during meetings, establishing the principles of scoring, and confirming the accuracy of the evidence level assessments, providing preliminary recommendation level suggestions. Then, all 15 consensus members voted to make the final consensus decision on the recommendation levels, followed by external review conducted by experts from various countries and diverse fields, ultimately forming the guideline.

The strength of the recommendations considered the robustness of evidence, balance of benefits, patient preferences, and treatment costs to make a comprehensive suggestion. The strength of the recommendations was categorized into four levels based on expert opinions: "Very Strong," "Strong," "Moderate," and "Weak." "Very Strong" indicated a robust endorsement, non-adherence to which may lead to adverse outcomes or even clinical criticism. "Strong" was suggested when adherence to the recommendations brought substantial advantages and benefits with minimal drawbacks. "Moderate" signified a neutral stance, necessitating more evidence for a final decision, but currently not opposed by experts. "Weak" suggested opposition, where the disadvantages of adopting the strategy outweighed the benefits, causing a burden.

Evidence Quality Level	GRADE scoring (with an interval of 0.5)
High	4–3.5
Moderate	3–2.5
Low	2–1.5
Very Low	<1.5

Recommendation Strength	Expert Recommendation
Very Strong	Strongly advise adherence; non-compliance can lead to negative consequences and may even face clinical criticism.
Strong	Compliance with the recommendation can bring significant benefits with few drawbacks.
Moderate	Neutral stance; more evidence is needed for a decision, but at least currently, experts do not oppose.
Weak	Opposing stance; the downsides of adopting the strategy outweigh the advantages, causing a burden.

* GRADE: Grading of Recommendations Assessment, Development and Evaluation.

The aim of this study is to explore the application of PCT in the emergency department setting, examining various contexts of its use, including its role in intervention, diagnosis and treatment. To avoid limiting the scope of the investigation, this study is not a de novo meta-analysis. Instead, it reviews the existing evidence by using the GRADE approach. In addition, we will update this guideline if necessary in the future.

3. Recommendations

PCT-guided antibiotic stewardship

Literature Review

Antibiotic usage worldwide has significantly increased in the past two decades, and as a consequence of misuse, the proportion of antibiotic-resistant bacteria has been rising [11]. In 2019, approximately 4.95 million deaths were related to antibiotic-resistant bacteria, of which around 1.27 million deaths were directly attributable to antibiotic-resistant infections, with respiratory tract infections accounting for the majority of cases [12]. In 2021, the World Health Organization declared antibiotic-resistant bacteria as one of the top ten public health threats globally [13]. The goal of antibiotic stewardship is to achieve better patient care by ensuring the availability of antibiotics whenever needed, and to reduce the misuse or overuse of antibiotics. Clinically, empirical antibiotics are often administered based on various scientific society guidelines, and adjustments are made once the bacterial culture results are available. However, waiting for culture results is time-consuming, and bacterial cultures can present false-positive and false-negative cases. The production and release kinetics of PCT make it a potential reliable indicator for diagnosing infection and monitoring the effectiveness of antibiotic treatment. However, different disease states may affect the release and metabolism of PCT differently. Therefore, it is necessary to provide different recommendations for different disease groups.

Through database searches in PubMed and EMBASE, articles after December 2016 were selected, using keywords such as "procalcitonin antibiotics stewardship", "procalcitonin antibiotics emergency", "procalcitonin antibiotics", "procalcitonin emergency", and "procalcitonin guide antibiotic". The search results were limited to clinical studies, with no restrictions on publication time or language. In addition to the electronic medical literature database search, references from the literature were also used as a source of information. Case reports, comments, literature review articles, and guidelines were not included. A total of 767 articles were collected from PubMed and EMBASE. Based on the titles and abstracts, 742 articles were preliminarily excluded. After reading 25 full-text articles, 17 were excluded for various reasons detailed in Fig. 1, leaving 8 articles included in this discussion [18-27]. Respiratory diseases, fever, heart failure, urinary tract infections, and acute pancreatitis were the conditions included in the literature overview presented in Supplemental Table 1.

The selection of literature was limited to immunocompetent adults and did not include children and those with chronic infections. In fact, the scope of PCT-guided antibiotic use is not limited to the five diseases discussed in this article. For instance, PCT has high sensitivity and

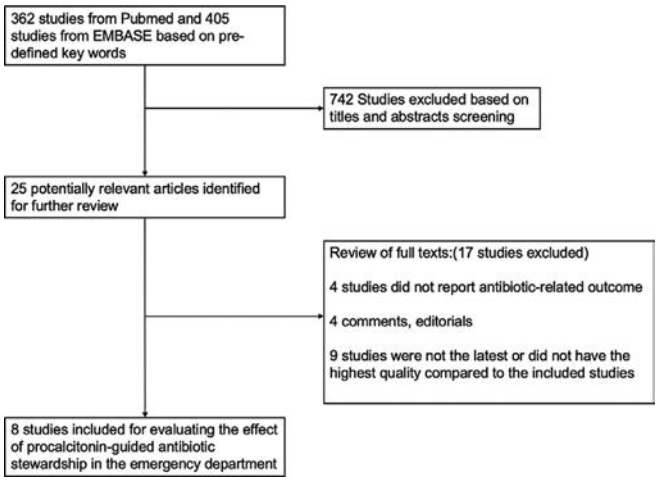
362 studies from Pubmed and 405 studies from EMBASE based on pre-defined key words
742 Studies excluded based on titles and abstracts screening
25 potentially relevant articles identified for further review
Review of full texts:(17 studies excluded)
4 studies did not report antibiotic-related outcome
4 comments, editorials
9 studies were not the latest or did not have the highest quality compared to the included studies
8 studies included for evaluating the effect of procalcitonin-guided antibiotic stewardship in the emergency department

Fig. 1. Study screening flowchart: PCT-guided antibiotic stewardship.

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specificity in determining bacterial meningitis [14]; however, there is currently a lack of clinical trials studying the variations in antibiotic dosages, and hence, studies on other diseases were not included in the discussion of this article.

Additionally, this article did not include a health economic analysis of PCT-guided antibiotic use. On one hand, some analyses based on real-world data suggested that PCT-guided antibiotic use can reduce hospitalization costs [15,16]. However, cost-effectiveness analyses based on randomized controlled studies did not support this conclusion [17]. Whether the conclusions in real-world studies can be attributed to the use of PCT remains controversial. On the other hand, there is currently a lack of local cost-effectiveness analysis in Taiwan. Therefore, more related health economic studies are needed in the future.

Recommendation 1. For patients presenting with lower respiratory tract infection symptoms in the emergency department, it is recommended to use PCT values as a basis for antibiotic use. It is recommended to use antibiotics when PCT concentration is > 0.25 ng/mL; conversely, evidence does not support using antibiotics based on PCT concentration below this level. (Moderate level of evidence, Strong recommendation strength).

Rationale for the Recommendation

There is still considerable debate regarding the appropriate PCT threshold levels for initiating antibiotic therapy. In a meta-analysis by Schuetz et al. (2017) [18], various respiratory infections and clinical scenarios were analyzed, incorporating 26 randomized controlled trials. Fourteen emergency use trials were subjected to subgroup analysis. The conclusion drawn was that under PCT guidance, the usage and side effects of antibiotics were reduced, while there were no significant differences in the 30-day mortality rate, hospitalization duration, and treatment failure rate. This conclusion was also applicable to individual diseases such as community-acquired pneumonia, acute exacerbations of COPD, and acute bronchitis. Hospitalized patients admitted through emergency departments and those non-hospitalized patients admitted to emergency departments exhibited similar results. However, the selected PCT thresholds in the chosen papers of this study were not consistent. Most studies recommended the use of antibiotics only if the PCT was above 0.25 ng/mL, while a minority used a higher threshold of 0.5 ng/mL or 1 ng/mL. However, in a RCT by Huang et al. [19], which was conducted in the United States and focused on patients in emergency settings with suspected lower respiratory tract infections utilizing PCT-guided antibiotic use, no significant difference in antibiotic use was found. This finding was inconsistent with the results of many previous studies. The PCT threshold used in this study was the following: "strongly advise against the use of antibiotics for PCT <0.1 ng/mL; advise against the use of antibiotics for 0.1~0.25 ng/mL; recommend the use of antibiotics for >0.25 ng/mL ~ 0.5 ng/mL; and strongly recommend the use of antibiotics for >0.5 ng/mL". These were the reference values published by the United States FDA and were the standards adopted by most respiratory disease research in recent years. Most of the commentary on this study believed that the lack of an antimicrobial stewardship program may be the reason for the low adherence to PCT guidelines by physicians in this study. For example, even though 92.3 % of patients had PCT concentrations indicating that the use of antibiotics was not recommended (<0.25 mg/L), 34.1 % of patients still received antibiotic treatment in the emergency department, and 57.0 % received antibiotic treatment within thirty days of admission. Additionally, insufficient experience of the physicians involved in the trial in using PCT could have also been one of the possible reasons.

Meanwhile, a 2019 RCT study targeted patients with community-acquired pneumonia in the emergency department [20]. The PCT usage threshold adopted was consistent with the standards used in the aforementioned study by Huang et al. This study found no significant differences between the two groups guided by PCT and those guided by IDSA/ATS guidelines in terms of antibiotic use duration, length of hospital stay, and severe side effects. Compared to the study by Huang et al., the physicians in this study had at least three years of experience using PCT, which reduced the intervention of the research team and was more in line with actual clinical situations.

In the risk of bias section of the meta-analysis by Schuetz et al. [18], more than 2/3 of the studies had a high risk in the blinding of outcome assessment, hence the risk of bias score was reduced by one point. There were no apparent inconsistencies, indirectness, imprecision, or publication biases, and the final result was given a score of 3, rated as a moderate level of evidence. Considering that this meta-analysis indicated that using PCT as a basis for guiding clinical decisions might reduce the use of antibiotics, it is recommended to use PCT, with a strong recommendation strength given.

However, considering the differences between the design of these studies and actual clinical practice, it is challenging to strictly adhere to PCT thresholds as the sole standard for administering antibiotic treatment without taking other clinical situations into account. In fact, it is reasonable to enhance PCT standards based on clinical criteria. More research is required to support the application of PCT thresholds in various scenarios. Misdiagnosing patients with suspected lower respiratory tract infections as pneumonia and administering antibiotics could not only increase the risk of adverse drug reactions, but also lead to unnecessary costs. More critically, the effort to find the correct diagnosis might be hindered, consequently delaying the time to attain the correct diagnosis and treatment. Similarly, if pneumonia would be erroneously ruled out in patients with suspected lower respiratory tract infections, and antibiotics would not be administered timely, it could result in a worse clinical prognosis. Hence, we advocate for more refined clinical research in various scenarios to determine a more scientific PCT threshold or provide additional clinical indicators to aid clinical decision-making.

Recommendation 2. For patients experiencing an acute exacerbation of COPD in the emergency department, solely using PCT values as a basis for antibiotic use may not reduce antibiotic prescriptions and may not improve patient outcomes. (Moderate level of evidence, Moderate recommendation strength).

Rationale for the Recommendation.

Pázmány et al. (2021) in their meta-analysis showed that the sensitivity of PCT in diagnosing COPD exacerbations was 54 %, and the specificity was 71 %, with a significant increase in false negatives [21]. The heterogeneity was 96.2 %, necessitating a one-point deduction; there were no significant risks of bias, inconsistency, imprecision, or publication bias, and the final result was rated as a moderate level of evidence, scoring 3 points.

Mathioudakis et al. (2017) conducted a meta-analysis of 8 RCTs focusing on acute exacerbations of COPD [22]. Their conclusion was that PCT-guidance could effectively reduce the probability and duration of antibiotic use, with no significant differences in treatment failure rate, relapse rate, and mortality rate. Although the study population in this meta-analysis mostly consisted of hospitalized patients rather than emergency patients, no downgrade was applied for indirectness since the conditions of both groups during acute exacerbations of COPD were similar. Due to the high risk in blinding of participants and personnel in more than two-thirds of the cases, a one-point deduction was made for the risk of bias; no significant inconsistencies, imprecisions, and publication biases were found, yielding a final score of 3 points, rated as a moderate level of evidence.

Chen et al. (2020) conducted a meta-analysis study focusing on acute exacerbations of COPD, including 5 RCTs [23]. The conclusion was that PCT-guidance did not reduce the duration of antibiotic use, and there were no significant differences in treatment failure and mortality rates. Although most of the study populations in this meta-analysis were hospitalized patients, not emergency patients, no downgrade was applied for indirectness as both groups had similar conditions during acute exacerbations of COPD. For the risk of bias, a one-point deduction was made because only 5 relatively low-risk RCTs were selected for analysis, resulting in a small sample size and a potential selection bias. There were no significant inconsistencies, imprecisions, and

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publication biases, yielding a final score of 3 points, rated as a moderate level of evidence.

In patients with acute exacerbations of COPD, infection is a common cause of disease worsening. Although there are meta-analysis reports indicating a significant increase in false negatives in the PCT diagnosis of COPD, utilizing PCT values as a basis for the appropriate use of antibiotics can improve patients' symptoms and prognosis, as well as reduce antimicrobial resistance and adverse reactions due to overuse. Therefore, a moderate recommendation strength is suggested clinically.

Recommendation 3. For patients presenting with a fever in emergency departments, evidence does not support only relying on PCT values of 0.5 ng/mL as a basis for antibiotic use. (High level of evidence, Strong recommendation strength).

Recommendation 4. For patients presenting with suspected heart failure in the emergency department, evidence does not support that using PCT alone as a guide for antibiotic prescription could alter physicians' antibiotic prescribing behavior or patient outcomes. (High level of evidence, strong recommendation).

Rationale for the Recommendations 3 and 4

The HiTEMP study conducted by Y. van der Does et al., a multicenter RCT, investigated the effect of PCT-guided antibiotic use in emergency fever patients (>38.2C) [24]. The study found that PCT did not reduce the rate of antibiotic use, and there were no significant differences in safety outcomes such as mortality rate and hospitalization rate. We believe that the high heterogeneity among febrile patients might lead to these non-significant results. There was no significant bias in this study, and the final score was 3.5, rated as a high level of evidence. The PCT threshold in this study was 0.5 μg/L (0.5 ng/ml), which was considered a higher threshold in clinical research. A single PCT measurement value cannot accurately diagnose bacterial infections. Therefore, it is strongly recommended not to use the PCT value of 0.5 ng/mL alone as the basis for antibiotic use, with a strong recommendation intensity.

A recent large-scale multicenter randomized clinical trial, IMPACT EU, studied patients in the emergency department who presented with symptoms suspicious of acute heart failure and elevated NT-proBNP levels, assessing the effect of using PCT as a guide for antibiotic use [25]. It was suggested to use antibiotics when the concentration was greater than 0.2 ng/mL and not recommended when it was less than 0.2 ng/mL. The results showed no significant effect; there was no significant difference in mortality rates at 30 and 90 days. Therefore, it was not recommended to use PCT in emergency patients with symptoms of acute heart failure. The study speculated that the lack of significant findings could be due to some participating physicians in IMPACT EU making unauthorized adjustments in clinical procedures, resulting in an adherence rate of only 83 %. Adherence refers to the extent to which a clinical trial complies with the research protocol. An adherence rate less than 100 % indicates that the treatment approaches of the study participants did not fully comply with the standards designed by the research protocol, thereby affecting the results of the study.

For emergency patients visiting due to fever or patients with heart failure, current evidence suggests that the use of PCT does not help to reduce the amount of antibiotics used. There are also no significant differences in the length of hospital stay and the rate of adverse effects. Therefore, it is not recommended to use the PCT value alone as a basis for guiding antibiotic use.

Recommendation 5. For patients with pyelonephritis accompanied by fever in emergency departments, guiding antibiotic use based on PCT levels combined with the presence of pyuria can significantly reduce the antibiotics usage without affecting prognosis. (Moderate level of evidence, moderate recommendation strength).

Rationale for the Recommendation

Daniel Drozdov et al. (2015) conducted a single-center RCT focusing on emergency patients with suspected urinary tract infections (UTIs), utilizing PCT-guided antibiotic use [26]. The study found that PCT could effectively reduce antibiotic usage by up to 30 %, and there were no significant differences in mortality and recurrence rates. The effectiveness of using PCT was less pronounced in the group with uncomplicated UTIs, but it was more significant in complicated cases accompanied by symptoms such as fever and pyelonephritis. PCT (threshold: 0.25 ng/mL) could be used in conjunction with the degree of pyuria as a basis for medical management and intervention.

This study, due to its small sample size ($N = 125$), exhibited issues of imprecision. The antibiotic use within 90 days in the control group was 10 days (interquartile range (IQR): 7–16 days), while it was 7 days in the experimental group (IQR: 5–14 days), showing significant overlap in the IQRs between the two groups. The 95 % confidence intervals (CIs) for mortality and recurrence rates were quite wide, with the former being 0.03–2.30 and the latter being 0.52–2.75, warranting a deduction of one point. No other significant biases were identified, resulting in a final score of 2.5, rated as a moderate level of evidence.

In clinical practice, for patients with complicated UTIs, PCT-guided antibiotic use can more effectively control the infection and reduce the risk of disease worsening. However, in the population with uncomplicated UTIs, there is no significant treatment effect, thus resulting in a moderate recommendation strength.

Recommendation 6. For patients with acute pancreatitis in the emergency department, it is recommended to use PCT values as a basis for antibiotic use. If the PCT concentration is > 1.0 ng/mL, antibiotic use is recommended; otherwise, it is not advised. (High level of evidence, strong recommendation strength).

Rationale for the Recommendation

Acute pancreatitis is not uncommon in emergency departments, yet physicians currently lack effective tools to distinguish between simple inflammation and bacterial infection, and thus to guide the use of antibiotics. A single-center RCT (PROCAP) in 2022 studied the guidance of antibiotic use by procalcitonin (PCT) levels in acute pancreatitis patients in emergency departments. PCT concentrations were tested on days 0, 4, and 7, with a threshold set at 1.0 ng/mL. Antibiotics were recommended to be initiated or continued if above this threshold, and not recommended or suggested to be discontinued if below this threshold. The results found that PCT could effectively reduce the rate and duration of antibiotic use, while there were no significant differences in mortality rate, reinfection rate, side effects, and length of hospital stay [27]. This study also excluded patients undergoing cholecystectomy, who require prophylactic antibiotics preoperatively. Siriwardena et al. (2022) conducted an RCT that demonstrated no substantial biases, ultimately receiving a score of 3.5, which signifies high-quality evidence.

For patients with acute pancreatitis, continuous dynamic monitoring of PCT holds significant clinical importance due to the predominantly non-infectious inflammatory responses in the early stages. PCT not only enables the determination of the onset of infection, but also allows for the assessment of the effectiveness of antibiotic treatments. Given its substantial clinical utility, the use of PCT comes with a strong recommendation.

Including PCT in the diagnosis of septic patients

Literature Review

Sepsis is a significant disease in emergency medicine, imposing a tremendous burden on global healthcare. Its incidence rate is steadily rising each year and, according to the Global Burden of Disease (GBD) 2017 report, it is estimated that there are approximately 48.9 million cases globally, with sepsis-related deaths accounting for 19.7 % of global mortality [28]. Even though early diagnosis and treatment are essential to reduce the mortality rate of sepsis, up to now, there still are not any well-established diagnostic criteria.

Bacteremia refers to the presence of bacteria in the bloodstream, triggering systemic inflammatory response symptoms, potentially leading to organ dysfunction and even life-threatening conditions. Clinically, the assessment of sepsis requires evaluation from three aspects: infection, inflammatory response (Systemic Inflammatory Response Syndrome, SIRS), and organ dysfunction. Among them, determining the presence or absence of infection is the core of treatment. According to

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the Sepsis-3 definition, the judgment of whether an infection is present often solely relies on the physician's assessment, which means that the accuracy and precision of the diagnosis can differ among different physicians. Due to the extensive clinical application of biomarkers, including PCT, we believe that combining biomarkers with inflammatory response indicators and disease severity could enhance the diagnostic accuracy of sepsis.

A search was conducted through two general literature databases, PubMed and EMBASE, using the keywords “procalcitonin”, “diagnosis”, “sepsis”, and “emergency”. The search results were further filtered using additional keywords, including “diagnosis”, “sepsis”, “emergency”, and “ED” to identify literature specifically related to the diagnosis of sepsis and relevant to emergency medicine studies. The search was restricted to clinical studies, with no limitations on publication dates and regions. Ultimately, seven studies were obtained, where six of them fell under the category of emergency medicine studies, five were meta-analyses, and two were cohort studies [29-35]. The five meta-analyses focused on scenarios where PCT was used alone, while the last two incorporated clinical indicators (see Fig. 2 and Supplemental Table 2). Because the studies involving PCT combined with SIRS (Systemic Inflammatory Response Syndrome) or SOFA (Sequential [Sepsis-related] Organ Failure Assessment) scores in diagnosing sepsis were observational in nature, they were considered to have a lower level of evidence.

Recommendation 7. Evidence does not support only relying on PCT as a marker for diagnosing sepsis in the emergency department; it is advised to incorporate other indicators for a combined diagnosis (Low level of evidence, Strong recommendation).

Rationale for the Recommendation

In the meta-analysis by Tang et al. (2007) [29], the authors demonstrated that in 14 research papers with low heterogeneity, the combined positive predictive value and negative predictive value of PCT were only moderate. This indicated that when PCT is used as a standalone test for diagnosis, the test results cannot accurately differentiate between severe patients with sepsis and SIRS. In the meta-analysis by Wacker et al. (2013) [30], involving a total of 3244 patients, the results obtained for the diagnosis of sepsis using PCT likewise indicated that PCT cannot serve as the sole criterion for diagnosing severe sepsis in patients. However, the study suggested that PCT, as a relatively better indicator, still has valuable reference merit and should be used in conjunction with a careful evaluation of patient history and physical examination for decision-making. All five meta-analyses showed that there are still uncertainties in diagnosing sepsis using PCT alone, and it should only be used in consideration with clinical symptoms or other indicators along with the physician's judgment. In the meta-analysis by Tang et al. [29], the index test's red-light interval ranged between 1/3 and 2/3, hence the error risk was reduced by 0.5 points. Since the emergency studies did not reach 1/3, it was downgraded by 0.5 points; with an I^2 of 88 %, it was downgraded by 1 point. There were no apparent inaccuracies or publication biases, resulting in a final score of 2 points, and it was rated as a low level of evidence. In the meta-analysis by Wu et al. (2017) [31], the high risk in the index test exceeded 2/3, hence the error risk was decreased by 1 point; with both sensitivity and specificity of I^2 being above 50 %, it was downgraded by 1 point. There were no significant indications of indirectness, imprecision, or publication bias, resulting in a final score of 2 points, fulfilling criteria for a substantial downgrade to a low evidence level. Clinically, incorporating other diagnostic tools can enhance the safety of PCT diagnosis, making this a strong recommendation.

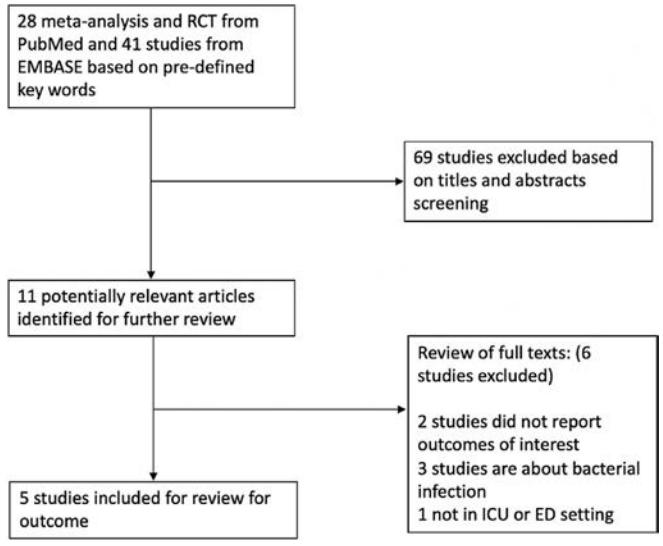
28 meta-analysis and RCT from PubMed and 41 studies from EMBASE based on pre-defined key words
69 studies excluded based on titles and abstracts screening
11 potentially relevant articles identified for further review
Review of full texts: (6 studies excluded)
2 studies did not report outcomes of interest
3 studies are about bacterial infection
1 not in ICU or ED setting
5 studies included for review for outcome

Fig. 2. Study screening flowchart: PCT in the diagnosis of septic patients.

This recommendation is also in line with the 2021 Surviving Sepsis Campaign (SSC) guidelines, which issued a weak recommendation against using a single PCT level on admission to guide antimicrobial initiation in patients with sepsis or septic shock. In a very high risk situation with high probability of bacterial infection, the focus should be on immediate treatment. However, the guidelines recommend that PCT should be used in conjunction with clinical evaluation to decide when to discontinue antimicrobials because this strategy has been shown to be effective in improving treatment and clinical outcomes in several trials. Thus, initial start of antimicrobial treatment based on clinical grounds only and later de-escalation based both on clinical assessment and PCT is the recommended approach in the high-risk patient population.

Recommendation 8. The accuracy of diagnosing sepsis using SIRS criteria can be enhanced by integrating PCT test results (Low level of evidence, Moderate recommendation strength).

Rationale for the Recommendation

The cohort study by Hicks et al. (2014) showed that adding PCT to the SIRS criteria can enhance the effectiveness of sepsis diagnosis [34]. There were no significant risks of bias, inconsistency, indirectness, imprecision, or publication bias, resulting in a final score of 2 points. Therefore, it was classified as a low level of evidence. Considering the lower level of evidence, there was not enough confidence in this recommendation. However, the definition of SIRS is broad, and non-bacterial causes of SIRS, such as viral infections, hematological malignancies, or autoimmune diseases, are quite common in clinical settings. The early and correct use of antibiotics is beneficial for the prognosis of sepsis. Therefore, considering adding PCT values based on the inflammatory response as a clue to the source of the inflammatory response could provide better accuracy and effectiveness in diagnosing sepsis without significantly increasing the clinical or economic burden. Thus, there was no opposition to this recommendation, making it a moderate recommendation strength.

Recommendation 9. When diagnosing sepsis, it is recommended to use PCT in conjunction with qSOFA scoring to increase sensitivity and specificity (Low level of evidence, Strong recommendation strength).

Rationale for the Recommendation

Bolanaki et al. (2021) in their cohort study demonstrated that in patients with elevated qSOFA scores, the utilization of PCT for diagnostic purposes could enhance the efficacy of sepsis diagnosis [35]. Additionally, there were no apparent risks of bias, inconsistency, indirectness, imprecision, or publication bias in their findings. The final score was 2, indicating a lower level of evidence. Given this lower evidence level, the expert team advocated for future high-quality clinical research in relevant areas. Considering the relationship between the SOFA score and organ dysfunction, the urgency of treatment differs between suspected sepsis patients with elevated SOFA scores and sepsis patients defined solely by SIRS. The qSOFA score is currently defined in Sepsis-3

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and can be assessed clinically using available values, enhancing the convenience for physicians. Therefore, even with a limited level of evidence, a strong recommendation was still advised.

Currently, there are only related studies on the combined diagnosis of sepsis using the qSOFA score and PCT values. The SOFA score and the National Early Warning Score (NEWS) are also equally important. There are existing studies confirming the efficacy of the SOFA score and NEWS in diagnosing sepsis. Notably, some research suggested that NEWS is more effective than qSOFA in diagnosing sepsis [36]. Moreover, studies have indicated that the combined use of the SOFA score and PCT provides good predictive efficacy for prognosis [37]. Therefore, SOFA and NEWS play significant roles in the diagnosis of sepsis and, together with PCT, constitute an essential direction for future developments in sepsis diagnosis. However, due to the complexity of the SOFA scoring, it is not easily implemented in emergency settings. Currently, there are no diagnostic studies incorporating PCT into the SOFA score. Given the clinical significance of PCT in bacterial infections and severity, it is still recommended to combine the SOFA score with PCT to enhance sensitivity and specificity.

Impact of diseases on the diagnostic performance of PCT

Literature Review

The false positivity of PCT may occur in patients with severe trauma, surgery, burns, those receiving immunomodulators, thyroid tumors, severe liver diseases and autoimmune diseases. False negatives tend to occur in localized or chronic infections. We searched two databases, PubMed and EMBASE, for articles published after January 2013. The keywords used were 'procalcitonin', 'diagnosis', and 'infection'. The search was limited to clinical studies including systematic literature reviews and meta-analyses, with no restrictions on language, country, or region. In addition to database searches, reference lists of articles were also used as sources of information. Case reports, comments, literature review articles, and guidelines were not included. Initial assessment of the data was based on the titles and abstracts, followed by a full-text review for further filtering. Selection criteria included statistical tests for the diagnostic utility of PCT in diagnosing sepsis, with results including false negatives and false positives in different patient groups or specific disease etiologies. Ultimately, 14 studies were included in the final evaluation [21,38-48,54,58]. Fig. 3 shows the flowchart of the selection process. Selected studies had to explicitly specify different patient groups or specific infectious diseases, using PCT as a diagnostic tool, and provide false-negative and false-positive test analysis. In this section, if sensitivity or specificity were below 70 %, it was considered reduced sensitivity or specificity. Summaries of the literature contents and recommendations are included in Table 1.

Recommendation 10. For patients who have undergone gastrointestinal surgery, there is an increased incidence of false positives in PCT diagnosis, leading to reduced diagnostic efficacy. For those who have had cardiac surgery, evidence does not suggest a significant increase in either false positives or false negatives. (Moderate evidence level, moderate recommendation strength).

Recommendation 11. For the diagnosis of sepsis in burned patients, evidence does not suggest a significant increase in either false negatives or false positives in PCT-based infection detection. (Moderate evidence level, moderate recommendation strength).

Rationale for the Recommendations 10 and 11

Trauma and surgery may lead to an elevation in PCT levels. This can explain the noticeable decrease in diagnostic specificity of PCT following gastrointestinal surgery, as well as a slight decrease following cardiac surgery or in cases of burns. Recommendations are made with a moderate degree of strength, taking into consideration the following points [38-40]:

1. Acknowledge the impact of surgery and trauma on the diagnostic efficacy of PCT. Even if current meta-analyses show minimal variation in diagnostic specificity after cardiac surgery and in cases of burns, these interfering factors should be considered in the clinical application of PCT.
2. PCT measurement may be employed as a supplementary diagnostic tool in identifying infections subsequent to surgery or in instances of burns. Nevertheless, predominant emphasis should be placed on the clinical manifestations and presentations in diagnostic deliberations.
3. When considering the application of PCT, a single measurement value is not reliable. The clinical significance of the dynamic changes in PCT may be more considerable.

Recommendation 12. For febrile patients with neutropenia, there is a significant increase in false negatives in PCT testing. Evidence does not support it as a tool to rule out infections. (Moderate evidence level, strong recommendation strength)

Recommendation 13. In patients with systemic lupus erythematosus, there could be a significant increase in false negatives when using PCT for infection diagnosis. (Moderate evidence level, moderate recommendation strength).

Rationale for the Recommendations 12 and 13

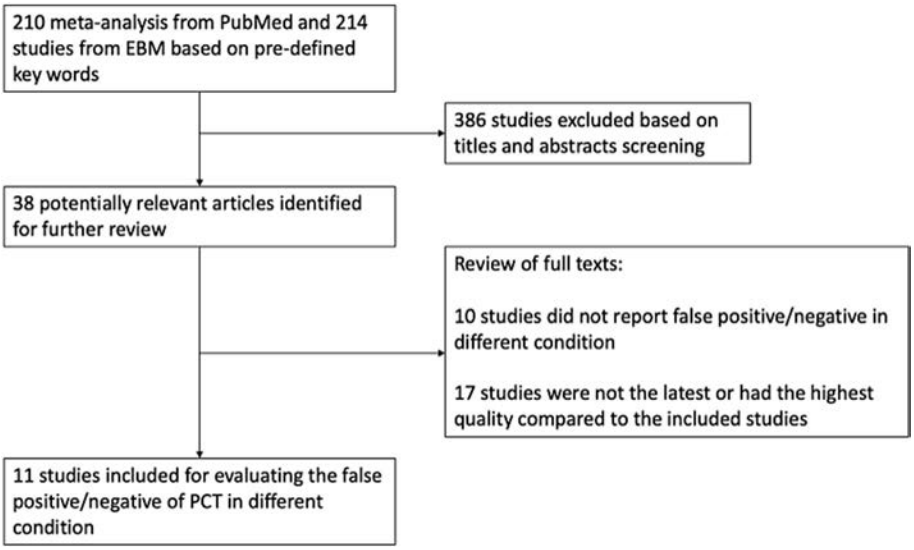
210 meta-analysis from PubMed and 214 studies from EBM based on pre-defined key words
386 studies excluded based on titles and abstracts screening
38 potentially relevant articles identified for further review
Review of full texts:
10 studies did not report false positive/negative in different condition
17 studies were not the latest or had the highest quality compared to the included studies
11 studies included for evaluating the false positive/negative of PCT in different condition

Fig. 3. Study screening flowchart: Impact of diseases on the diagnostic performance of PCT.

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Table 1
Diagnostic Performance of Procalcitonin (PCT) Testing in Various Clinical Conditions.

Clinical condition	Source	Study Type	Type of Infection	Results	Reason for upgrade/ downgrade	Occurrence of false positives/false negatives	Recommendation
Gastrointestinal surgery	Jerome et al. 2022	Meta-analysis ($N = 1611$)	Any infection	Sensitivity 0.72 (95 % CI: 0.66–0.78) Specificity 0.62 (95 % CI: 0.59–0.64)	Presence of heterogeneity	Increased false positive	For patients who have undergone gastrointestinal surgery, there is an increased incidence of false positives in PCT diagnosis, leading to reduced diagnostic efficacy. For those who have had cardiac surgery, there is no significant increase in either false positives or false negatives. (Moderate evidence level, moderate recommendation strength)
Cardiac surgery	Li et al.2021	Meta-analysis (14 studies)	Any infection	Sensitivity 0.81 (95 % CI: 0.75–0.87) Specificity 0.78 (95 % CI: 0.73–0.83)	Presence of heterogeneity	No	For patients undergoing cardiac surgery, there is no significant increase in false positives or false negatives. (Moderate evidence level, moderate recommendation strength)
Burns	Li et al. 2022	Meta-analysis (28 studies)	Sepsis	Sensitivity 0.73 (95 % CI: 0.53–0.87) Specificity 0.75 (95 % CI: 0.66–0.82)	Presence of heterogeneity	No	In burn patients, for the diagnosis of sepsis, there is no significant increase in either false negatives or false positives in PCT-based infection detection. (Moderate evidence level, moderate recommendation strength)
Immunodeficiency	Hoeboer et al. 2015	Meta-analysis (N = 16,514)	Bacteremia	Sensitivity 0.66 (95 % CI: 0.54–0.76) Specificity 0.78 (95 % CI: 0.71–0.83)	Presence of heterogeneity	Increased false negative	For patients with immunodeficiency, there is a significant increase in false-negative PCT. It is not recommended as a tool to rule out infection. (Moderate evidence level, strong recommendation strength)
	Wu et al. 2015	Meta-analysis (27 studies)	Bacterial infection	Sensitivity 0.67 (95 % CI: 0.54–0.77) Specificity 0.86 (95 % CI: 0.80–0.91	Presence of heterogeneity	Increased false negative	
Systemic lupus erythematosus (SLE)	Bruera et al. 2022	Meta-analysis (26 studies)	Any infection	Sensitivity 0.68 (95 % CI: 0.059–0.77) Specificity 0.75 (95 % CI: 0.59–0.90)	Presence of heterogeneity	Increased false negative	For patients with SLE, there is a significant increase in false negatives when using PCT for infection diagnosis. (Moderate evidence level, moderate recommendation strength).
Bone and joint infection	Tang et al. 2022	Meta-analysis ($N = 45,316$)	Periprosthetic joint infection	Sensitivity 0.57 (95 % CI: 0.43–0.7) Specificity 0.9 (95 % CI: 0.79–0.95)	Presence of heterogeneity	Increased false negative	For patients with bone and joint infections, there is a significant increase in false negatives when using PCT for diagnosis. PCT is not suitable for exclusion due to these false negatives. However, PCT has high specificity and can be considered as a tool for confirmation. (Moderate evidence level, moderate recommendation strength)
	Shen et al. 2013	Meta-analysis ($N = 583$)		Sensitivity 0.67 (95 % CI: 0.37–0.88) Specificity 0.90 (95 % CI: 0.78–0.96)	Presence of heterogeneity	Increased false negative	
Infective endocarditis (IE)	Yu et al. 2013	Meta-analysis (6 studies)		Sensitivity 0.64 (95 % CI: 0.52–0.74) Specificity 0.73 (95 % CI: 0.58–0.84)	Presence of heterogeneity	Increased false negative	For patients suspected of having IE, there is a significant increase in false negatives when using PCT for diagnosis. PCT is not suitable as an exclusion tool. (Moderate evidence level, strong recommendation strength)

95 % CI: 95 % confidence interval.

Hoeboer et al. (2015) centered their study on patients with fever and neutropenia and included those undergoing chemotherapy for cancer [41], while Wu et al. (2015) strictly focused on patients experiencing fever and neutropenia [42]. PCT plays a nuanced role in diagnosing infections in patients with compromised immunity. Opportunistic infections like fungal infections may mildly elevate PCT levels, providing some discernment in diagnosing bacterial or fungal infections. However, this also introduces additional complicating factors when utilizing PCT as a diagnostic marker for bacterial infections. Based on available evidence, a strong recommendation is made to consider PCT levels in

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diagnosing infections in patients with fever and neutropenia. However, using PCT as the sole diagnostic criterion or basing the diagnosis on a single PCT measurement is advised against.

For autoimmune diseases presenting with fever, such as systemic lupus erythematosus (SLE), discerning whether the symptoms stem from the primary autoimmune activity or an infection is crucial. Certain studies, such as the one referenced [43], have indicated that PCT possesses modest utility in this differential diagnosis, albeit with limited efficacy. Given the current evidence, a moderate level of recommendation is accorded to the use of PCT in diagnosing SLE, allowing its use as a component in the evaluative framework, with a special emphasis on accounting for variations in diagnostic sensitivity.

Recommendation 14. In patients with osteoarticular infections, evidence suggests a significant increase in false negatives when using PCT for infection diagnosis. Its efficacy in ruling out infections is limited, but it has high specificity and can be used as a diagnostic tool. (Moderate evidence level, moderate recommendation strength).

Rationale for the Recommendation

Regarding bone and joint infections, existing evidence indicates that the sensitivity of PCT in diagnosis is relatively low. However, in Shen et al.'s meta-analysis (2013), subgroup analyses were conducted based on varying diagnostic thresholds [45]. Results indicated that employing a lower diagnostic threshold (0.2–0.3 ng/mL) yielded a sensitivity of 0.90 and a specificity of 0.87 in diagnosing bone and joint infections. This underscores the enhanced specificity of PCT in the diagnosis of bone and joint infections, implying its utility in confirming such infections. Conversely, considering that different thresholds can be chosen to augment the sensitivity of infection diagnosis, integrating these with clinical parameters can also aid in exclusionary diagnostic approaches. Therefore, a recommendation of moderate strength has been given.

Recommendation 15. In patients suspected of having infective endocarditis, there is a significant increase in false negatives when using PCT for diagnosis. Evidence does not support PCT as a tool for exclusion. (Moderate evidence level, strong recommendation strength).

Rationale for the Recommendation

Infective endocarditis (IE) is commonly caused by Gram-positive cocci. Studies have shown that the elevation of PCT levels induced by Gram-positive cocci infections is lower than that caused by Gram-negative bacilli [47]. Current evidence suggests that the sensitivity of PCT in diagnosing IE is significantly reduced, and its specificity is also not high. Therefore, it is strongly recommended not to use PCT as a marker for diagnosing IE. PCT is advised not to be used as a tool for exclusionary diagnosis. Hence, a strong recommendation strength is given against the utilization of PCT as an exclusionary tool in the diagnosis of IE.

Application of PCT in special patient populations

Literature Review

This section reviews the conditions that might affect the metabolism of PCT in the body, focusing on patients with a high risk of infection, including those with: (1) renal insufficiency, (2) hepatic dysfunction, and (3) organ transplant recipients. The kidneys are one of the primary pathways for the elimination of PCT from the body. Previous studies have shown that patients with severe renal insufficiency have significantly lower urinary PCT concentrations. Although renal elimination is reduced, the correlation between plasma clearance rates and renal dysfunction is weak. Therefore, clinical decisions based on PCT plasma concentrations are likely not to be affected [49-51].

This section does not include patients undergoing continuous renal replacement therapies such as Continuous Veno-Venous Hemofiltration (CVVH) and Continuous Veno-Venous Hemodialysis (CVVHD). Some studies have shown that the clearance of PCT in patients undergoing CVVHD with high cut-off hemofilters may be influenced by the renal replacement therapy [52]. The liver, besides being capable of producing PCT, also has been shown in studies to influence the metabolism of PCT within the body when there is liver injury [53]. This article is solely focused on adult patients with cirrhosis and does not include those with acute liver injuries, post-liver surgery patients, or pediatric patients. Patients with cirrhosis are also at high risk of infections; spontaneous bacterial peritonitis (SBP) is a common infectious complication among them. Moreover, infections in patients with cirrhosis can easily lead to severe complications such as hepatic encephalopathy, resulting in death. In organ transplant patients, due to their compromised immune function, early diagnosis and treatment of bacterial infections are particularly crucial.

We used PubMed and EMBASE for research. For patients with renal insufficiency, the search keywords “renal insufficiency” and “procalcitonin” were used, yielding six results. Through title filtering, one article was retained, and meta-analysis articles citing this paper were searched, resulting in two final inclusions. For patients with liver dysfunction, the search keywords were “liver disease” and “procalcitonin”, producing eleven results. One article remained after title screening, and one more was included after filtering the meta-analysis articles citing it, making up two articles in total. For organ transplant patients, the search keywords were “transplantation”, “transplant”, and “procalcitonin”, yielding eight results. After title screening, three articles remained, with no additional cited literature. Hence, a total of seven meta-analysis reports were included across all specified groups [54,56-61], as represented in Fig. 4 and Supplemental Table 3.

Due to a lack of randomized controlled trials and meta-analyses specifically targeted at these patients, the evaluation of evidence in this section primarily focuses on examining whether PCT significantly improves sensitivity or specificity in the detection of bacterial infections. Therefore, the recommendation level does not include considerations such as clinical prognosis or the amount of antibiotic usage. Different clinical studies used different diagnostic thresholds. In some meta-analyses, subgroup analyses were conducted based on various diagnostic thresholds, with 0.5 ng/ml commonly used as a standard evaluation threshold.

1. **Renal insufficiency**

Recommendation 16. For patients undergoing hemodialysis, it is recommended to use PCT testing as a basis for determining the presence of bacterial infections. (Low evidence level, strong recommendation strength)

Recommendation 17. For patients undergoing hemodialysis, PCT threshold values of > 1.5 ng/mL and 0.85 ng/mL may be considered for confirming and excluding bacterial infections, respectively. (Low evidence level, weak recommendation strength).

Rationale for the Recommendations 16 and 17

Patients undergoing hemodialysis are at high risk for bacterial infections. Early diagnosis of related infections allows for immediate antibiotic treatment, thus reducing possible complications. The meta-analysis by Tao et al. (2022) demonstrated a sensitivity of PCT in detecting bacterial infections in patients receiving hemodialysis of 0.9 (95 % confidence interval: 0.85–0.94); a specificity of 0.83 (95 % confidence interval: 0.56–0.95) and an AUROC of 0.92 (95 % confidence interval: 0.90–0.94) [54]. The results were comparable to the data in the general population with normal renal function of the meta-analysis by Simon et al. (2004) (sensitivity: 0.88; 95 % confidence interval: 0.80–0.93; specificity: 0.81; 95 % confidence interval: 0.67–0.90) [55]. If the PCT threshold is set between 0.685 ng/mL to 0.85 ng/mL, although a good pooled sensitivity result (0.95; 95 % confidence interval: 0.84–0.99) can be obtained, the pooled specificity is only 0.77 (95 % confidence interval: 0.68–0.83). Conversely, if the threshold is set between 1.5 ng/mL to 15.5 ng/mL, a higher pooled specificity (0.89; 95 % confidence interval: 0.81–0.94) is achieved, which can better confirm the diagnosis of bacterial infection in patients undergoing hemodialysis treatments [54].Tao et al. (2022) showed that over 2/3 of the patient selection

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was at high risk, hence the risk of bias was reduced by 1 point; an I^2 of 88 % led to a downgrade of 1 point; there was no obvious indication of indirectness, imprecision, or publication bias, resulting in a final score of 2 points, and it was rated as low-level evidence.

Considering that the meta-analysis by Tao et al. (2022) showed that PCT performs well concerning the sensitivity and specificity in diagnosing infection, even though the level of evidence is somewhat low, it is still highly recommended to use PCT to assist in the diagnosis of infection [54]. This recommendation indicates that, in patients undergoing hemodialysis, there is no need to additionally consider whether the factor of renal insufficiency should be accounted for in using PCT for infection diagnosis. However, it is worth noting that using a higher threshold (1.5 ng/ml) offers better positive and negative likelihood ratios compared to a lower threshold (0.85 ng/mL), while the AUROC is similar. The diagnostic efficacy of using the common threshold of 0.5 ng/mL is inferior. Thus, based on the results of Tao et al. [54] it seems to suggest that a higher diagnostic/exclusion threshold should be used in dialysis patients. However, considering the poor prognosis of hemodialysis patients after infection, a threshold with higher sensitivity (0.85 ng/mL) is still chosen as the standard for ruling out infection. Due to the stronger heterogeneity of this meta-analysis, there is a lower degree of mastery regarding the related thresholds. Therefore, it is recommended to adopt a weaker recommendation strength, meaning that in principle, only referring to these thresholds is suggested, and comprehensive clinical evidence should be taken into consideration.

Recommendation 18. For patients undergoing peritoneal dialysis, PCT testing can be used as a basis for confirming bacterial peritonitis, but it may not be suitable for excluding the possibility of peritonitis. (Moderate level of evidence, moderate recommendation strength)

Rationale for the Recommendation

Peritonitis remains a major complication of peritoneal dialysis, with high mortality and morbidity rates. Although microbiological culture is considered the gold standard for diagnosis, issues such as reporting delays and high false-negative rates have been reported. The utilization of PCT testing could significantly reduce the waiting time for laboratory reports.

Lu et al. (2013) [56] in a meta-analysis demonstrated that for patients undergoing peritoneal dialysis, PCT has a considerably high specificity (0.91; 95 % confidence interval [CI]: 0.84–0.95) in detecting bacterial peritonitis. However, it has a lower sensitivity (0.53; 95 % CI: 0.39–0.66). Yang et al. (2014) [57] in their meta-analysis included the five studies on peritoneal dialysis patients from the Lu et al. (2013) [56] meta-analysis, and also incorporated patients with hepatic cirrhosis-related peritonitis. The literature indicated that for 391 patients undergoing peritoneal dialysis, PCT had a lower sensitivity in detecting peritonitis (sensitivity: 0.64; 95 % CI: 0.47–0.78), but a higher specificity (specificity: 0.91; 95 % CI: 0.85–0.94). However, both were not as effective as PCT in diagnosing spontaneous peritonitis in patients with cirrhosis (sensitivity: 0.86; 95 % CI: 0.81–0.89, specificity: 0.94; 95 % CI: 0.85–0.97). Yang et al. (2014) had a high risk in 1/2 of the index tests, and a high risk in 1/2 of the flow and timing analysis, hence the risk of bias was reduced by 1 point. There was no significant indirectness, inconsistency, imprecision, or publication bias, so the final result was 3 points, rated as moderate evidence level. Lu et al. (2013) had a high risk in 1/3 of the index tests, and a high risk in 1/2 of the flow and timing analysis, hence the risk of bias was reduced by 1 point; with an I^2 of 63.1 %, it was downgraded by 1 point. There was no significant indirectness, imprecision, or publication bias, so the final result was 2 points, rated as low evidence level.

In the two meta-analyses by Yang et al. [57] and Lu et al. [56], most studies used 0.5 ng/ml as the diagnostic threshold. For peritoneal dialysis-related peritoneal infections, current evidence suggests that the sensitivity of PCT in diagnosing peritoneal dialysis-related peritonitis is lower, but specificity is higher. Therefore, it is not recommended to use it as a tool for exclusion diagnosis, but it can be used as a reference for diagnosis. Whether the diagnostic performance can be improved by adjusting the diagnostic threshold still needs further research. The overall recommendation strength suggests being skeptical when evaluating the role of PCT in diagnosing peritoneal dialysis-related peritonitis, but it can be used as one of the diagnostic indicators.

2. **Liver dysfunction**

Recommendation 19. For patients with liver cirrhosis, it is recommended to use PCT testing to determine the presence of bacterial infections. (Low evidence level, strong recommendation strength).

Recommendation 20. If spontaneous bacterial peritonitis is suspected in patients with liver cirrhosis, it is recommended to use PCT testing as a basis for confirmation. (Low evidence level, strong recommendation strength).

Rationale or the Recommendations 19 and 20

The results of a meta-analysis by Lin et al. in 2014, which included 1144 patients with cirrhosis, showed that the AUROC for diagnosing bacterial infections in patients with cirrhosis was 0.92 (95 % CI: 0.89–0.94), the sensitivity was 0.79 (95 % CI: 0.64–0.89), and the specificity was 0.89 (95 % CI: 0.82–0.94) [58]. In contrast, the sensitivity for patients with normal liver function was 0.88 (95 % CI: 0.80–0.93) and the specificity was 0.81 (95 % CI: 0.67–0.90) [55]. This confirms that the diagnostic performance of PCT testing in patients with cirrhosis is not significantly worse than in patients with normal liver function. Additionally, the result of PCT testing for systemic infection in patients with cirrhosis (sensitivity: 0.74; 95 % CI: 0.53–0.88; specificity: 0.91; 95 % CI: 0.82–0.95) is comparable to the diagnostic performance in patients with normal liver function. Lin et al. (2014) had a 1/3 high risk in the index testing part, and a 1/2 high risk in the timing and flow part, leading to a reduction of one point in the risk of bias; there was no obvious indirectness, inconsistency, imprecision, or publication bias, hence the final result was rated as 3 points, equivalent to a moderate evidence level.

Yang et al. [57] and Lin et al. [58] in their respective meta-analyses, explored subgroups of patients with SBP triggered by cirrhosis. The results of the meta-analysis by Lin et al. showed that for PCT the sensitivity is 0.88 (95 % CI: 0.70–0.95), specificity is 0.83 (95 % CI: 0.68–0.91), and the AUROC is 0.92 (95 % CI: 0.89–0.94) [58]. In Lin et al. (2014) [58], the index test had a 1/3 high risk, and the timing aspect had a 1/2 high risk, resulting in a decrease of 1 point due to risk of bias; an I^2 of 66.2 % led to a downgrade of 1 point. There was no significant indirectness, imprecision, or publication bias, hence the final score was 2, rated as low evidence level. The results from Yang et al., based on 807 patients, showed a sensitivity of 0.86 (95 % CI: 0.81–0.89), specificity of 0.94 (95 % CI: 0.85–0.97), and AUROC of 0.91 (95 % CI: 0.89–0.94). In Yang et al. (2014), the index test part had a 1/2 high risk, and the flow and

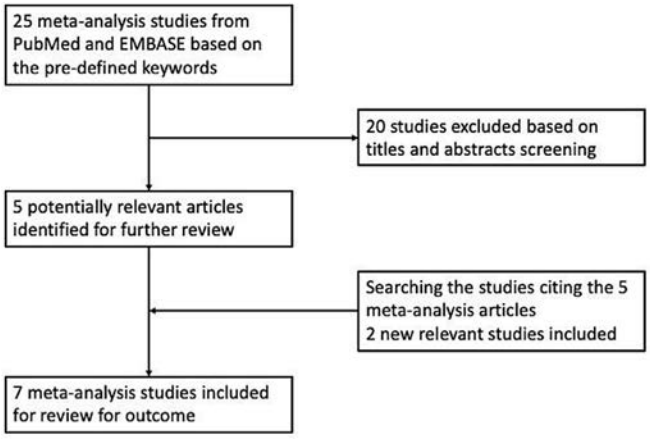
25 meta-analysis studies from PubMed and EMBASE based on the pre-defined keywords
20 studies excluded based on titles and abstracts screening
5 potentially relevant articles identified for further review
Searching the studies citing the 5 meta-analysis articles
2 new relevant studies included
7 meta-analysis studies included for review for outcome

Fig. 4. Study screening flowchart: application of PCT in special patient populations.

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timing analysis part also had a 1/2 high risk, resulting in a 1-point deduction due to risk of bias; an I^2 of 80.65 % resulted in a 1-point downgrade. There was no apparent indirectness, imprecision, or publication bias, hence the final score was 2, categorized as a low level of evidence. The findings from the two meta-analyses were consistent with the results from Simon et al. (2004) for patients with normal liver function, showing a sensitivity of 0.88 (95 % CI: 0.80–0.93) and a specificity of 0.81 (95 % CI: 0.67–0.90) [55].

Although impaired liver function may affect PCT concentrations, current meta-analyses indicate that PCT has good diagnostic efficacy in patients with cirrhosis, including those with SBP due to cirrhosis. In the studies by Yang et al. [57] and Lin et al. [58], subgroup analyses using a diagnostic threshold of 0.5 ng/mL both showed good diagnostic performance (AUROC both above 0.9). The evidence presented supports a high sensitivity and specificity of PCT in diagnosing infections in patients with cirrhosis, leading to a strong recommendation despite the slightly lower level of evidence. This strong recommendation indicates that in patients with cirrhosis, the impact of liver dysfunction on the decision to use PCT for infection diagnosis does not need special consideration. However, for other scenarios of impaired liver function, more evidence is still needed for support.

3. **Organ transplantation**

Recommendation 21. For patients who have undergone solid organ transplantation, it is recommended to use PCT testing to determine the presence of infectious complications. (Moderate evidence level, strong recommendation strength).

Recommendation 22. For patients who have undergone hematopoietic stem-cell transplantation, evidence does not support using PCT testing as a diagnostic tool for bacterial infections. (Moderate evidence level, strong recommendation strength).

Rationale for the Recommendations 21 and 22

Yu et al. (2014) meta-analysis indicated that PCT testing has moderate sensitivity and specificity in diagnosing infectious complications in patients who have undergone solid organ transplantation [59]. The AUROC was 0.90 (95 % CI: 0.87–0.92), the sensitivity was 0.85 (95 % CI: 0.75–0.92), and the specificity was 0.81 (95 % CI: 0.72–0.88). These results were consistent with previous meta-analyses conducted on general (non-transplant) hospitalized patients with bacterial infections, where the sensitivity was 0.88 (95 % CI: 0.80–0.93) and the specificity was 0.81 (95 % CI: 0.67–0.90) [55]. In Yu et al. (2014), the index test part had a 1/3 high risk, and the timing analysis part had a 1/2 high risk, leading to a deduction of 1 point for the risk of bias; the Deek's test *P*-value was 0.03, leading to a 0.5-point deduction for publication bias. No apparent indirectness, inconsistency, or imprecision was observed, resulting in a final score of 2.5, which was rated at a moderate evidence level.

In Lyu et al. (2013) meta-analysis [60], which focused on patients undergoing hematopoietic stem cell transplantation, the sensitivity of PCT for bacterial infections was 0.66 (95 % CI: 0.60–0.72), the specificity was 0.72 (95 % CI: 0.65–0.79), and the AUROC was 0.69 (95 % confidence interval: 0.65–0.73). This study included both adults and children, and in the subgroup analysis of adult patients, the diagnostic specificity of PCT was even lower (0.69, 95 % CI: 0.63–0.75). Compared to patients who did not undergo organ transplantation, the results were less favorable. Therefore, PCT is not suitable as a diagnostic tool for confirming bacterial infections in patients undergoing hematopoietic stem cell transplantation. The index test in Lyu et al. (2013) had a 1/3 high-risk assessment, and the timing analysis had a 1/2 high-risk assessment, resulting in a 1-point reduction in the risk of bias. No signs of indirectness, inconsistency, imprecision, or publication bias were evident, resulting in a final score of 3, indicating a moderate level of evidence.

Diagnosing and treating infections in organ transplant and immunocompromised patients presents specific challenges. Firstly, immunosuppressive agents like corticosteroids can influence the synthesis of infection markers such as C-reactive protein, with some evidence suggesting that PCT may be less affected by immunosuppressive therapy [61]. Additionally, infections in immunocompromised patients often involve a more complex pathogen profile. While bacterial infections remain common, there is an increased risk of opportunistic infections like fungal infections. PCT primarily responds to bacterial endotoxins, resulting in only a mild increase in PCT levels during fungal infections, much less than seen in bacterial infections [61]. These factors give PCT a somewhat distinctive role in this patient population, but also introduce potential interference when using it to diagnose bacterial infections.

Based on current evidence, it is still advisable to consider PCT as an adjunct indicator when diagnosing infections in immunocompromised individuals. Timely administration of appropriate antibiotic therapy is crucial, justifying a strong recommendation. Nevertheless, relying solely on PCT or making diagnoses based on a single PCT test result is discouraged. In the context of hematopoietic stem cell transplant patients, due to PCT's limited sensitivity and specificity, its use in diagnosis is generally unnecessary. Clinical standards should suffice, leading to a strong recommendation against using PCT as a diagnostic tool for bacterial infections in this immunocompromised patient group.

Combining PCT with molecular testing for respiratory viruses

Literature Review

Worldwide, the misuse of antibiotics is an increasingly concerning and significant issue. The Centers for Disease Control and Prevention (CDC) in the United States estimated that 30 to 50 % of antibiotics prescribed in outpatient settings are unnecessary. Concurrently, the CDC also estimated that about 30 % of hospitalized patients receive unnecessary or inappropriate antibiotic treatments [62]. As negative culture results are not uncommon among septic patients [63], pathogen-specific biomarkers are essential for diagnosing and managing sepsis, guiding antibiotic use, and predicting patient prognosis [64]. In this section, we focus on the combination of PCT with virus-specific biomarkers, given the growing challenge of managing suspected viral pneumonia in the emergency room during pandemics in the foreseeable future. Other pathogen-specific biomarkers (e.g., galactomannan) or host response biomarkers (e.g, C-reactive protein) were not included in this guideline. Although combinations of different biomarkers have not consistently shown better diagnostic performance than single biomarkers [65-67], rapid viral antigen tests hold great potential to improve antibiotic stewardship by providing accurate and timely diagnostic information. We believe that combining respiratory viral molecular testing with PCT could enhance the safety and effectiveness of antibiotic use, leading to reduced and more efficient antibiotic management.

We searched PubMed and EMBASE using keywords such as 'procalcitonin,' 'respiratory virus,' and 'antibiotic stewardship'. Results were cross-verified using additional terms like 'virus,' and 'antibiotic' to focus on studies relevant to viral molecular testing with PCT usage. A supplementary search using 'multiplex,' and 'respiratory virus' was conducted to ensure comprehensiveness. Our search focused on clinical studies without restrictions on publication dates or locations, resulting in the inclusion of five studies [68-72]. Out of the five articles, two were designed as emergency medicine-related studies, two were randomized clinical trials, and three were cohort studies, as detailed in Fig. 5. The characteristics and data of the five studies, as well as their effects on antibiotic management, can be seen in Supplemental Table 4.

Recommendation 23. For patients with respiratory infections, it is recommended to combine multiplex molecular tests for respiratory viruses with PCT testing. This aids in distinguishing between viral and bacterial infections, guiding the prescription of antibiotics. (Moderate evidence level, strong recommendation strength)

Rationale for the Recommendation

All five studies confirmed that for patients with respiratory infections, the use of PCT in combination with respiratory viral molecular testing could distinguish between viral and bacterial infections, and all were able to reduce antibiotic use. Among them, there were two single randomized clinical trials. Gilbert et al. (2016) studied 211 emergency

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department patients with community-acquired pneumonia, utilizing respiratory viral molecular testing (FilmArray) and procalcitonin testing [68]. They found a significant reduction in the duration of antibiotic treatment in the group tested with FilmArray ($P = 0.03$), demonstrating that combining molecular and PCT testing can optimize antibiotic use, supporting the enhancement of antibiotic stewardship activities. These findings encourage the expansion of rapid diagnostic tools to better determine pneumonia's etiology and improve antibiotic management. Branche et al. (2015) conducted a study involving 151 hospitalized patients, utilizing multiplex respiratory viral PCR testing [69]. The study observed a reduction in the duration of antibiotic use in subgroup analyses, indicating that the combination of PCT with respiratory viral molecular testing can effectively improve antibiotic management.

Gilbert et al. (2016) did not employ a double-blind approach, reducing the risk of bias score by one point. There were no significant inconsistencies, indirectness, imprecision, or publication bias, resulting in a final score of 3, rated as moderate evidence level. Branche et al. (2015) had significant differences in patient characteristics, reducing the risk of bias score by one point. Again, there were no notable inconsistencies, indirectness, imprecision, or publication biases, resulting in a final score of 3, rated as moderate evidence level. However, conducting a double-blind study in this research direction is challenging, and since the recommendation does not have major drawbacks, it holds a strong recommendation strength.

Lee et al. (2020) conducted a prospective cohort study targeting elderly patients aged 65 or above with severe respiratory infections [70]. The study combined multiplex respiratory viral molecular testing (FilmArray Multiplex PCR Respiratory Panel) and PCT testing, and the results were provided to clinicians for reference. Among 169 individuals in the experimental group and 507 in the control group, after final adjustments, it was found that the likelihood of discontinuation or de-escalation of antibiotics, the prescription probability of neuraminidase inhibitors, and the duration of intravenous antibiotic usage were reduced in the experimental group. This indicates that the utilization of viral molecular testing combined with PCT testing in elderly patients with severe respiratory infections can genuinely reduce the misuse of antibiotics. The cohort study results did not meet the significant upgrade conditions, therefore being rated as moderate evidence level. Despite the need to consider the current Taiwanese health insurance payment policies and the testing costs of multiplex respiratory PCR testing, the aforementioned approach could bring substantial advantages and benefits, thus holding a strong recommendation strength.

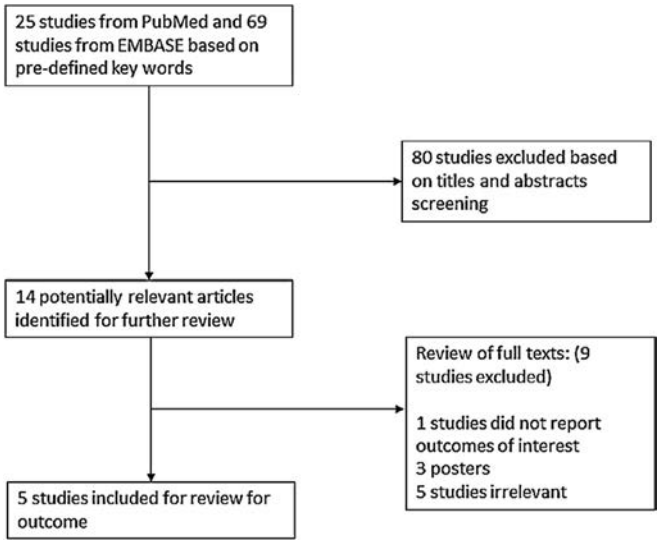
25 studies from PubMed and 69 studies from EMBASE based on pre-defined key words
80 studies excluded based on titles and abstracts screening
14 potentially relevant articles identified for further review
Review of full texts: (9 studies excluded)
1 studies did not report outcomes of interest
3 posters
5 studies irrelevant
5 studies included for review for outcome

Fig. 5. Study screening flowchart: combining PCT with molecular testing for respiratory viruses.

Timbrook et al. (2015) conducted a retrospective cohort study utilizing multiplex respiratory viral molecular testing to observe antibiotic usage based on positive viral molecular test results and low PCT values [71]. The study did not achieve significant results in reducing antibiotic usage, indicating that direct intervention with physicians is still necessary to improve inappropriate antibiotic prescriptions. The lack of significant differences might have been associated with the limitations of retrospective research. Despite the inconclusive findings of Timbrook et al. (2015) and the study's lower evidence level—with only 31 patients showing positive results in viral molecular testing and low PCT levels—the combination of PCT and multiplex molecular tests for respiratory viruses continues to be strongly recommended.

Recommendation 24. By using electronic medical record alert systems, for low PCT values and/or positive results from multiplex molecular tests for respiratory viruses, physicians can be reminded about the appropriateness of prescribing antibiotics, thus effectively preventing the improper use of antibiotics. (Low evidence level, strong recommendation strength).

Rationale for the Recommendation

Moradi et al. (2020) published a multicenter cohort study involving 226 patients, illustrating that the use of PCT combined with respiratory viral molecular testing, augmented by alert systems in medical records, could reduce antibiotic prescriptions [72]. The results revealed a significant reduction in the duration of antibiotic use and the proportion of prescriptions at discharge. Moradi et al. (2020) received a score of 2, signifying a low level of evidence, with no conspicuous risk of bias, inconsistency, indirectness, imprecision, or publication bias. The recommendation, while considering both PCT and viral molecular results and maintaining the physician's final decision authority, presents substantial benefits and minimal safety risks, making it a strong recommendation due to its advantages outweighing the drawbacks.

4. Conclusions

With the comprehensive review of the up-to-date evidence in application of PCT in emergency settings, the expert panel made practical recommendations tailored for the clinical practice. This document delves into PCT's roles in diagnosing sepsis, managing antibiotics, its concurrent use with respiratory virus molecular testing, and its applications for special patient cohorts and diverse disease contexts, with the goal of optimizing the management of patients with infection sepsis.

Even though PCT is a valuable biomarker and plays an important role in diagnosing sepsis and in antibiotic stewardship, its use necessitates consideration of its sensitivity and specificity within varied diseases and patient groups. Integrating PCT with additional markers, such as respiratory virus molecular assays, can enhance the accuracy of diagnostics. These guidelines are intended for use by health care professionals who care for patients at risk of sepsis caused by various infections, primarily emergency medicine physicians. However, it is important to notice that guidelines cannot always account for individual variation among patients. Thus, while recommending clinicians to adhere to the guidance set forth in this guideline, we encourage them to apply these guidelines with adaptability, informed by the specific conditions of the patient and prevailing antibiotic guidelines, to facilitate the best therapeutic monitoring and decision-making, thus optimizing the utility of PCT in patient care.

Summary of recommendations for guidelines

The recommendations for the guidelines are summarized as follows. For detailed information on methodology, background, and supporting evidence, please refer to the main text.

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The guidelines are divided into five main topics: (1) PCT-guided antibiotic stewardship, (2) Including PCT in the diagnosis of septic patients, (3) Impact of diseases on the diagnostic performance of PCT, (4) Application of PCT in special patient populations, and (5) Combining PCT with molecular testing for respiratory viruses.

PCT-guided antibiotic stewardship

1. For patients presenting with lower respiratory tract infection symptoms in the emergency department, it is recommended to use PCT values as a basis for antibiotic use. It is recommended to use antibiotics when PCT concentration is >0.25 ng/mL; conversely, evidence does not support using antibiotics based on PCT concentration below this level. (Moderate level of evidence, Strong recommendation strength).
2. For patients experiencing an acute exacerbation of COPD in the emergency department, solely using PCT values as a basis for antibiotic use may not reduce antibiotic prescriptions and may not improve patient outcomes. (Moderate level of evidence, Moderate recommendation strength).
3. For patients presenting with a fever in emergency departments, evidence does not support only relying on PCT values of 0.5 ng/mL as a basis for antibiotic use. (High level of evidence, Strong recommendation strength).
4. For patients presenting with suspected heart failure in the emergency department, evidence does not support that using PCT alone as a guide for antibiotic prescription could alter physicians' antibiotic prescribing behavior or patient outcomes. (High level of evidence, strong recommendation).
5. For patients with pyelonephritis accompanied by fever in emergency departments, guiding antibiotic use based on PCT levels combined with the presence of pyuria can significantly reduce the antibiotics usage without affecting prognosis. (Moderate level of evidence, moderate recommendation strength).
6. For patients with acute pancreatitis in the emergency department, it is recommended to use PCT values as a basis for antibiotic use. If the PCT concentration is >1.0 ng/mL, antibiotic use is recommended; otherwise, it is not advised. (High level of evidence, strong recommendation strength)

Including PCT in the diagnosis of septic patients

7. Evidence does not support only relying on PCT as a marker for diagnosing sepsis in the emergency department; it is advised to incorporate other indicators for a combined diagnosis (low level of evidence, Strong recommendation).
8. The accuracy of diagnosing sepsis using SIRS criteria can be enhanced by integrating PCT test results (low level of evidence, Moderate recommendation strength).
9. When diagnosing sepsis, it is recommended to use PCT in conjunction with qSOFA scoring to increase sensitivity and specificity (Low level of evidence, Strong recommendation strength).

Impact of diseases on the diagnostic performance of PCT

10. For patients who have undergone gastrointestinal surgery, there is an increased incidence of false positives in PCT diagnosis, leading to reduced diagnostic efficacy. For those who have had cardiac surgery, evidence does not suggest a significant increase in either false positives or false negatives. (Moderate evidence level, moderate recommendation strength).
11. For the diagnosis of sepsis in burned patients, evidence does not suggest a significant increase in either false negatives or false positives in PCT-based infection detection. (Moderate evidence level, moderate recommendation strength).
12. For febrile patients with neutropenia, there is a significant increase in false negatives in PCT testing. Evidence does not support it as a tool to rule out infections. (Moderate evidence level, strong recommendation strength)
13. In patients with systemic lupus erythematosus, there could be a significant increase in false negatives when using PCT for infection diagnosis. (Moderate evidence level, moderate recommendation strength).
14. In patients with osteoarticular infections, evidence suggests a significant increase in false negatives when using PCT for infection diagnosis. Its efficacy in ruling out infections is limited, but it has high specificity and can be used as a diagnostic tool. (Moderate evidence level, moderate recommendation strength).
15. In patients suspected of having infective endocarditis, there is a significant increase in false negatives when using PCT for diagnosis. Evidence does not support PCT as a tool for exclusion. (Moderate evidence level, strong recommendation strength).

Application of PCT in special patient populations

16. For patients undergoing hemodialysis, it is recommended to use PCT testing as a basis for determining the presence of bacterial infections. (Low evidence level, strong recommendation strength)
17. For patients undergoing hemodialysis, PCT threshold values of >1.5 ng/mL and 0.85 ng/mL may be considered for confirming and excluding bacterial infections, respectively. (Low evidence level, weak recommendation strength).
18. For patients undergoing peritoneal dialysis, PCT testing can be used as a basis for confirming bacterial peritonitis. However, its effectiveness in excluding peritonitis is relatively poor. (Moderate evidence level, moderate recommendation strength).
19. For patients with liver cirrhosis, it is recommended to use PCT testing to determine the presence of bacterial infections. (Low evidence level, strong recommendation strength).
20. If spontaneous bacterial peritonitis is suspected in patients with liver cirrhosis, it is recommended to use PCT testing as a basis for confirmation. (Low evidence level, strong recommendation strength).
21. For patients who have undergone solid organ transplantation, it is recommended to use PCT testing to determine the presence of infectious complications. (Moderate evidence level, strong recommendation strength).
22. For patients who have undergone hematopoietic stem-cell transplantation, evidence does not support using PCT testing as a diagnostic tool for bacterial infections. (Moderate evidence level, strong recommendation strength).

Combining PCT with molecular testing for respiratory viruses

23. For patients with respiratory infections, it is recommended to combine multiplex molecular tests for respiratory viruses with PCT testing. This aids in distinguishing between viral and bacterial infections, guiding the prescription of antibiotics. (Moderate evidence level, strong recommendation strength).
24. By using electronic medical record alert systems, for low PCT values and/or positive results from multiplex molecular tests for respiratory viruses, physicians can be reminded about the appropriateness of prescribing antibiotics, thus effectively preventing the improper use of antibiotics. (Low evidence level, strong recommendation strength).

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Evidence Quality Level	GRADE scoring (with an interval of 0.5)
High	4–3.5
Moderate	3–2.5
Low	2–1.5
Very Low	<1.5

Recommendation Strength	Expert Recommendation
Very Strong	Strongly advise adherence; non-compliance can lead to negative consequences and may even face clinical criticism.
Strong	Compliance with the recommendation can bring significant benefits with few drawbacks.
Moderate	Neutral stance; more evidence is needed for a decision, but at least currently experts do not oppose.
Weak	Opposing stance; the downsides of adopting the strategy outweigh the advantages, causing a burden.

* GRADE: Grading of Recommendations Assessment, Development and Evaluation.

CRediT authorship contribution statement

Chien-Chang Lee: Conceptualization, Supervision, Methodology, Writing - Review & Editing, Resources. **Lorenzo Porta**: Investigation, Writing - Original Draft, Writing - Review & Editing. **Ye Liu**: Investigation, Writing - Original Draft, Writing - Review & Editing. **Pin-Tung Chen**: Literature Review, Visualization, Project Administration, Writing - Review & Editing. **Hung-Hsuan Pan**: Literature Review, Visualization, Project Administration, Writing - Review & Editing. **Yi-Tzu Lee**: Investigation, Writing - Review & Editing. **Kuan-Fu Chen**: Investigation, Writing - Review & Editing. **Ching-Chi Lee**: Investigation, Writing - Review & Editing. **Weide Tsai**: Investigation, Writing - Review & Editing. **Chorng-Kuang How**: Investigation, Writing - Review & Editing. **Chien-Cheng Huang**: Investigation, Writing - Review & Editing. **Kuan-Ho Lin**: Investigation, Writing - Review & Editing. **Chien-Chin Hsu**: Investigation, Writing - Review & Editing. **Chia-Te Kung**: Investigation, Writing - Review & Editing. **Sung-Yuan Hu**: Investigation, Writing - Review & Editing. **Yen-Ren Lin**: Investigation, Writing - Review & Editing. **Chin-Wang Hsu**: Investigation, Writing - Review & Editing. **Chih-Huang Li**: Investigation, Writing - Review & Editing. **Ming-Yuan Hong**: Investigation, Writing - Review & Editing. **Philipp Schuetz**: Supervision, Investigation, Writing - Review & Editing.

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Declaration of competing interest

The authors have no conflict of interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2024.11.093.

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